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Atrial fibrillation is associated with cognitive decline in stroke-free subjects: The Tromsø Study

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Abstract

Background: Previous studies have shown associations between atrial fibrillation (AF) and cognitive decline. We investigated this association in a prospective population study, focusing on whether stroke risk factors modulated this association in stroke-free women and men.

Methods: We included 4983 participants (57% women) from the 5th survey of the Tromsø Study (Tromsø 5, 2001), of whom 2491 also participated in 6th survey (Tromsø 6, 2007-08). Information about age, education, blood pressure, body mass index, lipids, smoking, coffee consumption, physical activity, depression, coronary and valvular heart disease, heart failure and diabetes was obtained at baseline. AF status was based on hospital records. The outcome was change in cognitive score from Tromsø 5 to Tromsø 6, measured by the verbal memory test, the digit-symbol coding test and the tapping test.

Results: Mean age at baseline was 65.4 years. The mean reduction in the tapping test scores was significantly larger in participants with AF (5.3 taps/10 sec, 95% confidence interval (CI) 3.9, 6.7) compared to those without AF (3.8 taps/10 sec, 95% CI 3.5, 4.1). These estimates were unchanged when adjusted for other risk factors and were similar for both sexes. AF was not associated with change in the digit-symbol coding or the verbal memory tests.

Conclusion: AF in stroke-free participants was independently associated with cognitive decline as measured with the tapping test.

Introduction

Atrial fibrillation (AF) is a common arrhythmia, associated with increased mortality and morbidity [1]. There is a decrease in the incidence and mortality of cardiovascular diseases (CVD), however AF prevalence does not follow this trend [2]. The number of AF patients is expected to rise due to better detection of silent AF, increasing age and conditions predisposing to AF [1]. The AF incidence increases with age and is higher in men [3].

AF increases the risk of stroke and heart failure. A growing body of evidence suggests AF as a risk factor for cognitive decline and dementia [2]. Several cross-sectional studies showed a positive association between AF and cognitive impairment [4, 5]. A meta-analysis including four cross-sectional and six prospective studies confirmed this association independent of stroke history [6].

The CHA_2DS_2-VASc score estimates stroke risk in non-anticoagulated AF patients by combining risk factors for stroke. Based on data from the Tromsø Study, we have previously shown that adding left atrial (LA) size to an elevated CHA_2DS_2-VASc score provided additional stratification of stroke risk [7]. In this study, we aimed to investigate the association between AF and cognitive function in a population study with six years of follow-up of stroke-free women and men. Furthermore, we investigated whether known stroke risk factors modulate this association.

Methods

Study population

The Tromsø Study is a prospective cohort study with a mainly Caucasian population [8] and includes seven surveys (1974 to 2016) referred to as Tromsø 1-7. Total birth cohorts and random population samples are invited, with 45473 individuals having participated in one or more survey. This study population constitutes subjects attending Tromsø 5 and 6, as cognitive testing started in Tromsø 5.

Eligible were participants in Tromsø 5 in 2001 (cross-sectional analysis) and in both Tromsø 5 and Tromsø 6 in 2007-08 (longitudinal analysis). In Tromsø 5, 8130 participants aged 30-89 years attended [8]. After exclusions, 4983 participants (57% women) were included for the cross-sectional analyses (Figure 1). Of these, 3409 subjects participated in Tromsø 6 and after exclusion, 2491 participants were included for the longitudinal analysis (Figure 1). The Tromsø Study has been approved by the Regional Committee for Medical and Health Research Ethics and the Norwegian Data Protection Authority. All participants have given written informed consent.

Baseline characteristics

Questionnaire data were used to define the covariates diabetes (yes/no), antihypertensive treatment (current/previous/never), smoking (current/previous/never), education, physical activity, depression and prevalent myocardial infarction (yes/no). Education was categorized as primary/secondary school, upper secondary school, college/university <4 years and college/university ≥4 years. Physical activity was categorized as active or sedentary. Body mass

index (BMI) was calculated as weight/height^2 (kg/m^2) and body surface area (BSA) was calculated by Du Bois formula ((Weight$^{0.425}$×Height$^{0.725}$)×0.007184). Blood pressure was automatically recorded three times with one-minute intervals after two minutes resting (Dinamap Vital Signs Monitor 1846, Criticon), and the mean from the last two readings was used. Hypertension was defined as systolic blood pressure ≥140 mmHg, diastolic blood pressure ≥90 mmHg or antihypertensive treatment.

Echocardiography

Echocardiography was performed by two cardiologists on a random subsample (n=1722) in Tromsø 5 [7], using the standard apical and parasternal long and short axis views. Standard 2D-guided M-mode registrations of anteroposterior LA size, internal dimensions of the LV and wall-thickness of the septum and posterior wall were made. Heart failure was defined as ventricular ejection fraction <50%.

CHA_2DS_2-VASc score

We calculated CHA_2DS_2-VASc score as follows; age (65-74: +1, ≥75: +2), sex (female ≥65: +1), history of congestive heart failure (+1), hypertension (+1), stroke/ transient ischemic attack / thromboembolism (+2), vascular disease (+1) and diabetes mellitus (+1) [7, 9]. Few subjects (1%) had heart failure in the echocardiography subsample. Thus, subjects without echocardiography were categorized as without heart failure.

Cognitive testing

We assessed cognitive function by three standardized tests, chosen because of their ability to detect early cognitive decline and their feasibility in screenings [10].

The twelve-word memory test tests short time verbal memory. Twelve nouns were shown written on a board and pronounced one at a time with five-second intervals [10]. The participants had two minutes to recall the words. One point was given for each word correctly recalled, giving the range from 0 to 12 points.

Digit-symbol coding test, a part of the Wechsler adult intelligence scale, was used to examine psychomotor speed, attention, and mental flexibility [10]. Rows containing small blank squares were each paired with a randomly assigned number from one to nine. Above these rows, a printed key paired each number with a different nonsense symbol. Following a practice trial, the subjects filled in as many as possible of the blank spaces with the corresponding symbol over 90 seconds.

Tapping test is a test mainly of psychomotor tempo. The subjects were instructed to tap as many times as possible for ten seconds with their index finger on a computer, which registered the number of taps. The task was repeated four times on both hands. The mean number of taps from the last three tests were used in the analyses [10]. Low test scores are defined as <4 for the verbal memory test, <12 for the digit-symbol coding test and <23 for the tapping test [11].

Atrial fibrillation

AF was documented by electrocardiogram based on a search of the diagnosis registry of the University Hospital of North Norway (outpatient clinic included) [12] (ICD-9 codes 427.0–427.99 and ICD-10 codes I47 and I48). For participants with a diagnosis of cerebrovascular or cardiovascular event without an arrhythmia diagnosis, text searches with ‘atrial fibrillation’ were performed. An independent endpoint committee adjudicated the events. All AF types were

merged. Participants with AF occurring only during an acute myocardial infarction, cardiac surgery, or in the last seven days of life, were not classified with AF.

Categorization of left atrial size

LA size was indexed by BSA and categorized as normal (<2.2 cm/m^2), moderately (2.2-2.79 cm/m^2) and severely enlarged (≥2.8 cm/m^2) LA.

Statistical analysis

We present sex stratified characteristics as means and standard deviation for continuous variables and proportions for categorical variables. Differences between groups were assessed by t-test and χ^2 test. Mean cognitive score in Tromsø 5 according to age groups, AF status and LA size adjusted for age, sex and education was estimated. Mean change in test scores from Tromsø 5 to 6 were estimated with multivariable linear regression, adjusted for baseline score, age, sex and education (model 1), and with further adjustments for total/HDL cholesterol ratio, BMI, hypertension and smoking (model 2). The echocardiography sub-sample was analyzed separately (model 3) using the same adjustments as in model 2 and with further adjustment for LA size (model 4). We confirmed the model assumptions by graphical inspection of residuals. We tested for interactions between age and AF, and sex and AF, for change in cognitive score, and for CHA_2DS_2-VASc score, AF and LA with sex and education for each cognitive test. Sex combined results are presented as sex-specific results were similar and no sex interaction was found. A two-sided p-value <0.05 was considered statistically significant. Statistical analysis was performed using STATA V.14 (Stata, College Station, Texas, USA).

Results

Baseline characteristics are presented in Table 1. The mean age was about 65 years for both sexes. Men had higher educational level, total/HDL cholesterol ratio and were more physically active. There was no sex difference in BMI and diabetes prevalence. Approximately 25% in both sexes were smokers. Hypertension, myocardial infarction and AF were more prevalent in men, but women had higher CHA_2DS_2-VASc score and higher prevalence of enlarged LA.

As the cognitive tests all had a distribution near normal, adjusted mean cognitive scores in Tromsø 5 (all participants and the sub-sample with repeated measurements) and adjusted mean changes in cognitive scores are shown in Table 2. The mean cognitive score was lower among older participants and in those with AF and enlarged LA. The decline in cognitive scores was similarly larger among those of older age, with enlarged LA size (statistically significant for the digit-symbol coding test) and among those with AF (statistically significant for the tapping test).

Table 3 shows change in cognitive score over 6 years by AF status. For subjects with AF, decline in cognitive test as measured by the tapping test was significantly (p=0.04) larger (-5.3 (95 % CI: -6.7,-3.9)) compared to those without AF (-3.8 (95 % CI: -4.1,-3.5)), and the same trend was seen for the digit-symbol coding test. Adjustment for other risk factors changed the estimates marginally. The log-likelihood ratio $\chi 2$ statistics for tapping test was not significant (p=0.16) when comparing models with and without risk factors. Adding depression and activity as co-variates in model 2 did not change the result, but reduced the number of participants due to missing values. When restricting the material to subjects with echocardiography (Model 3 and 4), the adjustment for LA size had no effect.

We also performed the analysis including CHA_2DS_2-VASc score together with AF in model 2 instead of age and sex. Baseline score and education were kept in the model. Furthermore, we re-analyzed the data by substituting CHA_2DS_2-VASc score with its individual components. The change in cognitive test scores associated with AF was similar and the main contributing components of the score were age and sex. In addition, we performed age and sex-stratified analyses, but only presented the non-stratified result due to lower statistical power.

Discussion

In this prospective population-based study of stroke-free subjects, we found that AF was significantly associated with 40% greater cognitive decline as measured by the tapping test. To our knowledge, no other population studies have examined the association between AF and cognitive decline using repeated standardized cognitive tests.

Our study confirms other studies in stroke-free subjects [13-15]. These studies mainly used the Mini-Mental State Examination (MMSE) or other established diagnostic criteria for evaluating cognitive function. The large prospective multi-national ONTARGET and TRANSCEND trials, found that participants with AF had a 14% increased risk of cognitive decline, defined as a decrease of 3 or more points in the MMSE test [16]. Similar results were found in studies among men [17, 18]. Another longitudinal study found no association between AF and cognitive decline [19]. ARIC (Atherosclerosis Risk in Communities) Study found an association between cognitive function and persistent AF [20].

Adjusting the association between AF and change in cognitive score for established risk factors did not change the conclusions. Additionally, when including the CHA_2DS_2-VASc score, we found that age and sex were the main contributing components. One study including subjects with and without stroke found CHA_2DS_2-VASc score as a significant predictor of dementia among AF patients [21]. Our study was among stroke-free participants and few had heart failure, vascular disease or diabetes, which might explain the result. Previously we found an increased stroke risk associated with LA enlargement, possibly due to increased risk of emboli, but adding LA size to our model did not affect the estimates. As only a subsample had measurements of LA size, the power to detect effects was low.

The association between AF and cognitive decline depends on the characteristics of the AF population. The association may not be directly related to AF, but could be due to an aging cohort with comorbidities. Several mechanisms may explain the association between AF and cognitive impairment, such as silent cerebral infarct, microemboli, microbleedings and cerebral hypoperfusion [22-26].

Finger tapping is an important test of cognitive function, as reduced motor speed is a sensitive marker of motor and cognitive cerebral dysfunction such as reduced manual dexterity, coordination and global performance [27]. One study found that motor slowing as indicated by finger tapping speed precede cognitive impairment [28]. Others found that stroke subjects compared to stroke-free subjects were best discriminated by impaired motor speed with non-dominant hand [29]. Finger tapping frequency was found to independently predict psychomotor slowing following stroke [30].

Strengths

Our study was performed in a large population of both sexes, with a high attendance rate, long follow-up and repeated assessments of sensitive cognitive tests that are feasible in a population screening [10]. Hospital data concerning stroke and AF underwent thorough case validation.

Limitations

Selection bias may occur because of lower participation rate among individuals with dementia. Participants with repeated cognitive testing were younger with better risk factor profile than those who were lost to follow-up. Though invited, institutionalized persons were probably not able to attend the 6th survey or to complete the questionnaires. Selection of subjects during data collection might have occurred, as 561 more participants completed the tapping test than the digit-symbol coding test in Tromsø 5 and it is likely that the proportion of subjects with cognitive impairment was higher among those who did not complete all tests. Information of AF and stroke was collected through linkage to the hospital diagnosis registry and the National Causes of Death Registry at Statistics Norway; this could have led to underestimation of non-fatal strokes and undiagnosed AF, if subjects were not hospitalized.

Conclusions

AF was independently associated with cognitive decline as measured with the tapping test in both sexes of stroke free subjects. Screening of AF patients for cognitive decline is warranted.

Conflict of Interest: None

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Figure Legend

Figure 1 Study population, The Tromsø Study 2001-2008

Table Legend

Table 1: Unadjusted baseline characteristics of the participants by sex. The Tromsø Study: Tromsø 5 (2001)

Table 2: Mean cognitive tests scores (95% confidence intervals (CI)) in Tromsø 5 and mean change in test scores between Tromsø 5 and Tromsø 6 by age, atrial fibrillation status and left atrial size. The Tromsø Study

Table 3 Mean (95 % confidence interval (CI)) change in cognitive test scores over 6 years according to atrial fibrillation (AF) status. The Tromsø Study

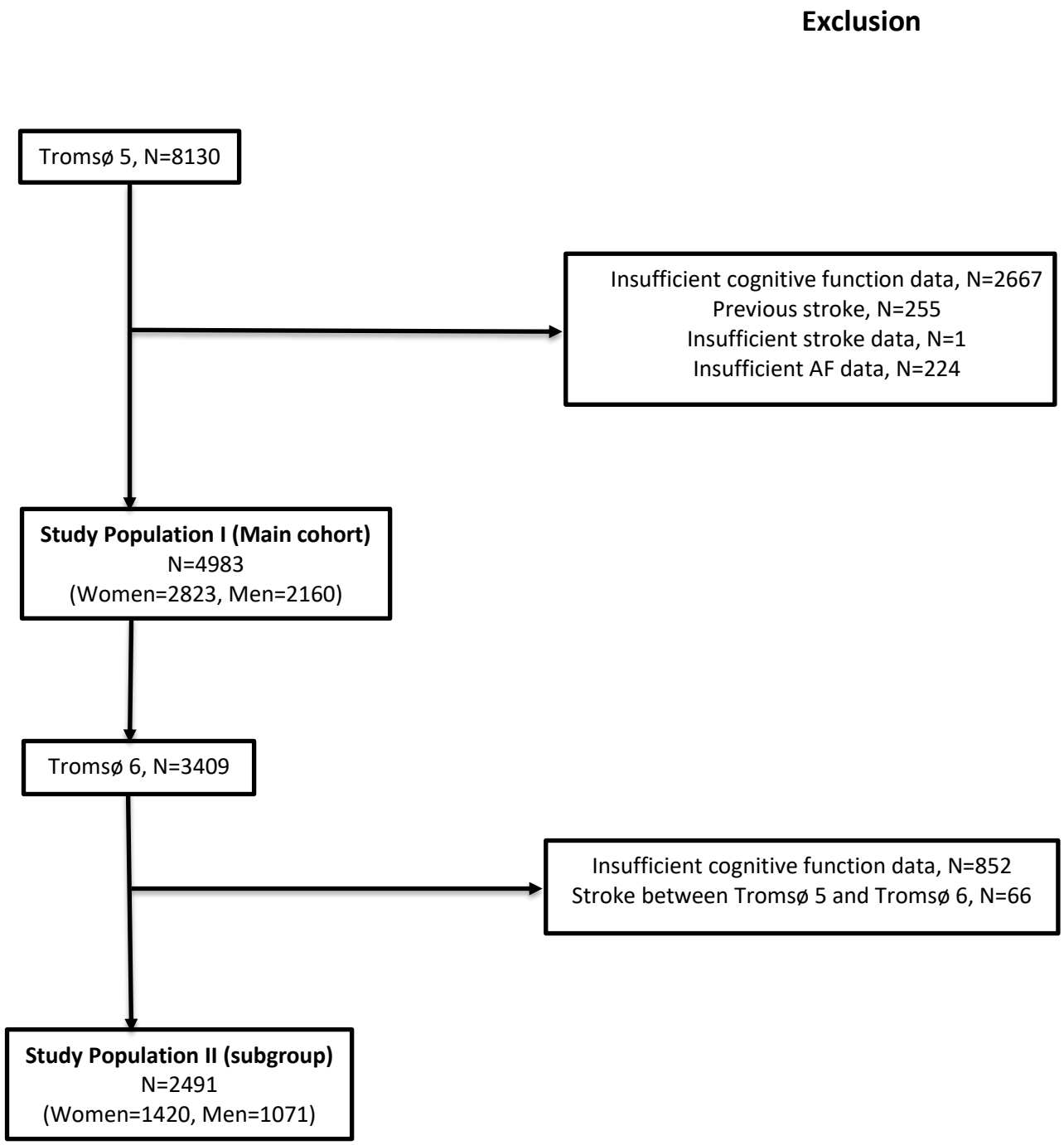

Figure 1 Study population, The Tromsø Study 2001-2008

Table 1: Unadjusted baseline characteristics of the participants by sex. The Tromsø Study: Tromsø 5 (2001)

Baseline characteristics	**Women (n=2823)**	**Men (n=2160)**	**p-value for sex-difference**
Age (years)	65.3 (9.8)	65.6 (9.3)	0.16
Education, % (n)			<0.0001
Primary and secondary school	59.9 (1600)	51.8 (1069)	
Upper secondary/high school	22.3 (594)	26.3 (543)	
College/university < 4 years	9.3 (247)	11.9 (245)	
College/university ≥ 4years	8.6 (229)	10.1 (208)	
Systolic blood pressure (mmHg)	143.0 (23.0)	143.2 (20.5)	0.83
Diastolic blood pressure (mmHg)	80.6 (13.0)	82.6 (11.9)	<0.0001
Body mass index (kg/m^2)	26.8 (4.6)	26.8 (3.5)	0.66
Total cholesterol (mmol/l)	6.51 (1.18)	6.09 (1.12)	<0.0001
HDL cholesterol (mmol/l)	1.59 (0.40)	1.36 (0.37)	<0.0001
Total/HDL- cholesterol ratio	4.31 (1.25)	4.78 (1.42)	<0.0001
Smoking, % (n)			<0.0001
No smoking	48.7 (1375)	23.1 (499)	
Previous smoking	27.1 (765)	52.4 (1131)	
Current smoking	24.2 (683)	24.5 (530)	
Physically active, % (n)	73.2 (1853)	80.9 (1674)	<0.0001
Hypertension, % (n)	60.4 (1705)	63.3 (1368)	0.04
Current antihypertensive treatment, % (n)	23.4 (641)	23.6 (498)	0.97
Depression, % (n)	3.8 (89)	1.4 (28)	<0.0001
CHA_2DS_2-VASc score, % (n)[a]			<0.0001
0	24.1 (680)	17.7 (382)	
1	19.3 (545)	31.4 (678)	
2	12.0 (339)	31.3 (675)	
3	27.5 (777)	16.1 (347)	
≥4	17.1 (482)	3.6 (78)	
Coronary heart disease, % (n)	3.8 (104)	11.8 (253)	<0.0001
Diabetes, % (n)	3.9 (107)	4.5 (97)	0.27
Atrial fibrillation, % (n)	2.9 (83)	4.9 (106)	<0.0001
Subsample with echocardiography data	**Women (n=885)**	**Men (n=837)**	
Left atrial size, % (n)			<0.0001
< 2.2 cm/m^2	43.5 (385)	59.0 (494)	
2.2-2.79 cm/m^2	52.1 (461)	37.5 (314)	
≥2.8 cm/m^2	4.4 (39)	3.5 (29)	

Number in the table referred as mean values (standard deviation) or % (number of subjects)
[a]CHA_2DS_2-VASc score: age (65-74: +1, ≥75: +2), sex (female ≥ 65: +1), history of congestive heart failure (+1), hypertension (+1), vascular disease (+1) and diabetes mellitus (+1)

Table 2: Mean cognitive tests scores (95% confidence intervals (CI)) in Tromsø 5 and mean change in test scores between Tromsø 5 and Tromsø 6 by age, atrial fibrillation status and left atrial size. The Tromsø Study

	Tromsø 5 (2001)[a]				**Change in test scores from Tromsø 5 to Tromsø 6 (95 % CI)[b] (n=2491)**	
	All participants (n=4983)		**Sub-sample with repeat measurement (n=2491)**			
	Mean (CI)	**p-value**	**Mean (CI)**	**p-value**	**Mean (CI)**	**p-value**
Verbal memory test[e]						
Age groups (years)		<0.0001[c]		<0.0001[c]		<0.0001[c]
<65	6.9 (6.8,7.0)		7.1 (7.0,7.2)		-0.2 (-0.3,-0.1)	
65-74	6.1 (6.0,6.2)		6.3 (6.2,6.4)		-0.9 (-1.0,-0.8)	
≥ 75	5.6 (5.5,5.7)		6.0 (5.7,6.3)		-1.5 (-1.7,-1.2)	
Atrial fibrillation		0.08		0.68		0.48
No	6.4 (6.3,6.4)		6.7 (6.6,6.8)		-0.6 (-0.6,-0.5)	
Yes	6.1 (5.9,6.4)		6.6 (6.1,7.1)		-0.4 (-0.7,-0.1)	
Left atrial size (cm/m^2)[d]		0.17[c]		0.22[c]		0.15[c]
< 2.2	6.4 (6.2,6.5)		6.7 (6.6,6.9)		-0.6 (-0.7,-0.4)	
2.2-2.79	6.2 (6.1,6.4)		6.5 (6.3,6.7)		-0.5 (-0.7,-0.3)	
≥2.8	6.0 (5.5,6.5)		6.3 (5.5,7.1)		-1.3 (-2.0,-0.5)	
Digit-symbol coding test[f]						
Age groups (years)		<0.0001[c]		<0.0001[c]		<0.0001[c]
<65	37.5 (37.0,38.1)		38.9 (38.2,39.6)		2.6 (2.1,3.2)	
65-74	28.6 (28.0,29.2)		30.1 (29.3,30.9)		-3.5 (-4.1,-2.8)	
≥ 75	23.2 (22.4,24.1)		26.4 (24.5,28.3)		-6.1 (-7.7,-4.4)	
Atrial fibrillation		0.05		0.15		0.22
No	31.7 (31.3,32.0)		34.7 (34.2,35.1)		-0.2 (-0.6,0.2)	
Yes	29.8 (27.9,31.7)		32.1 (28.5,35.6)		-1.3 (-2.9,0.4)	
Left atrial size (cm/m^2)[d]		0.05[c]		0.29[c]		0.01[c]
< 2.2	32.2 (31.4,33.0)		34.9 (33.9,36.0)		0.01 (-0.8,0.8)	
2.2-2.79	31.0 (30.1,31.8)		33.7 (32.5,34.9)		-1.9 (-2.8,-1.0)	
≥2.8	29.4 (26.5,32.2)		33.3 (28.4,38.3)		-3.4 (-7.5,0.8)	
Tapping test[g]						
Age groups (years)		<0.0001[c]		<0.0001[c]		<0.0001[c]
<65	54.6 (54.2,55.0)		55.0 (54.6,55.5)		-2.3 (-2.7,-1.8)	
65-74	50.7 (50.3,51.1)		51.4 (50.9,52.0)		-5.7 (-6.2,-5.1)	
≥ 75	46.4 (45.8,47.0)		47.6 (46.3,48.9)		-7.8 (-9.3,-6.4)	
Atrial fibrillation		0.08		0.99		0.04
No	51.7 (51.5,52.0)		53.1 (52.8,53.5)		-3.8 (-4.1,-3.4)	
Yes	50.5 (49.2,51.8)		53.1 (50.8,55.4)		-5.3 (-6.7,-3.9)	
Left atrial size (cm/m^2)[d]		0.12[c]		0.25[c]		0.34[c]
< 2.2	52.0 (51.4,52.6)		53.4 (52.6,54.2)		-3.5 (-4.2,-2.8)	
2.2-2.79	51.7 (51.0,52.3)		52.9 (52.0,53.8)		-4.0 (-4.8,-3.2)	
≥2.8	49.7 (47.5,51.9)		50.4 (46.8,54.1)		-5.8 (-9.3,-2.3)	

[a]Adjusted for age, sex and education. [b]adjusted for baseline score, age, sex and education
[c] P-value for linear trend [d]Left atrial size: subsample with echocardiography data (n=1722) in total sample, (n=875) in repeat measurement
[e]Scores are given as the number of correct words recalled (0-12). [f]Scores are given as the number of correct symbols coded (0-96). [g]Scores are given as the average number of taps in 10 second

Table 3 Mean (95 % confidence interval (CI)) change in cognitive test scores over 6 years according to atrial fibrillation (AF) status. The Tromsø Study.

	Change in test scores							
	Model 1		**Model 2**		**Model 3**		**Model 4**	
	Mean (CI)	**p-value**	**Mean (CI)**	**p-value**	**Mean (CI)**	**p-value**	**Mean (CI)**	**p-value**
Verbal memory test		0.48		0.41		0.42		0.37
No AF	-0.6 (-0.6,-0.5)		-0.6 (-0.6,-0.5)		-0.6 (-0.7,-0.4)		-0.6 (-0.7,-0.4)	
AF	-0.4 (-0.7,-0.1)		-0.4 (-0.7,-0.1)		-0.4 (-0.8,0.1)		-0.3 (-0.8,0.1)	
Digit-symbol coding test		0.22		0.23		0.77		0.89
No AF	-0.2 (-0.6,0.2)		-0.2 (-0.6,0.2)		-0.2 (-0.7,0.4)		-0.2 (-0.7,0.4)	
AF	-1.3 (-2.9,0.4)		-1.1 (-2.8,0.5)		-0.5 (-2.7,1.7)		-0.3 (-2.6,1.9)	
Tapping test		0.04		0.04		0.06		0.09
No AF	-3.8 (-4.1,-3.5)		-3.8 (-4.1,-3.5)		-3.3 (-3.8,-2.9)		-3.3 (-3.8,-2.9)	
AF	-5.3 (-6.7,-3.9)		-5.3 (-6.8,-3.9)		-5.2 (-7.1,-3.3)		-5.0 (-6.9,-3.1)	

Participants that have missing values in any one of the adjustment variables were excluded from analysis in all the models
Model 1: adjusted for baseline score, age, sex and educational level.
Model 2: adjusted for baseline score age, sex, educational level, Total/HDL cholesterol ratio, BMI, hypertension, smoking
Model 3: as Model 2 in the sub-sample with echocardiographic data (n= 873)
Model 4: as Model 2 with LA index added in the sub-sample with echocardiographic data (n= 873)